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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,901	02/02/2006	Mark Ashton	BJS-620-401	1869
23117 7590 08/23/2007 NIXON & VANDERHYE, PC 901 NORTH GLEBE ROAD, 11TH FLOOR ARLINGTON, VA 22203				
			EXAMINER CHANDRAKUMAR, NIZAL S	
			ART UNIT 1625	PAPER NUMBER
			MAIL DATE 08/23/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/556,901

Applicant(s)

ASHTON ET AL.

Examiner

Nizal S. Chandrakumar

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-31 and 34-50 is/are pending in the application.
- 4a) Of the above claim(s) 1-31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 34-50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The application filed 02/02/2006 and is a 371 of PCT/GB04/02101 05/14/2004.

Election/Restrictions

Applicant's response filed 06/26/2007 to restriction requirement is acknowledged.

In a telephonic (703-816-4091) conversation with the Attorney for the Applicant, Mr. B.J. Sadoff, the Examiner acknowledged the typographical errors in the Restriction Requirement in the previous office action. On 08/15/2007, Mr. Sadoff, confirmed the election of group VII drawn to claims 34-50 corresponding to compounds of formula I wherein X =CH, L2 is a single bond.

The Election was made with traverse. The applicant argues that the compounds of the prior art cited by the Examiner are not believed to be defined by the claims and therefore cannot anticipate the common structural feature of the instant claims. This is not found to be persuasive because the non-variable structural core of the instantly claimed compounds shares the same structural core of the compounds of the cited prior art establishing lack of unity.

The requirement is still deemed proper and is therefore made FINAL.

1. This application contains claims 1-31 drawn to an invention nonelected with traverse in Paper No. 06/26/2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
2. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1, Applicants have the limitations 'solvate'. What are the structures of these 'solvate? Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 34-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making four (two are esters and, two are acids corresponding to the esters) of the compounds of the claims, does not reasonably provide enablement for making the wide variety of compounds encompassed by the formula I as well as unknown solvates of the compounds of the formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. For instance, the specification is enabling the making of the compounds of the formula I wherein R1 is H. However the definition of R1 includes a large of number of variables. (Note: The COOH present in the working examples is not part of listed of variables in the definition of R1).

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

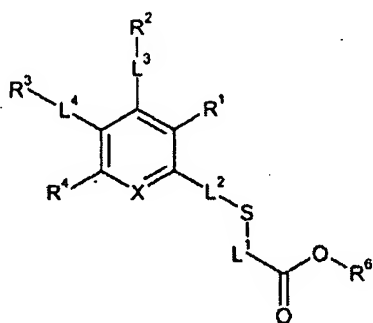
Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).

- 1) The breadth of the claims,
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

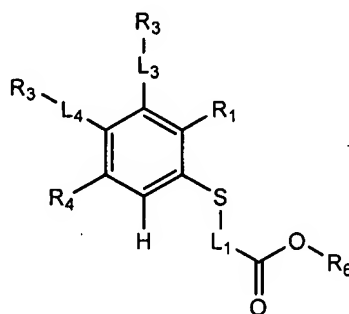
While all the above factors were considered, some of the specific considerations are described below:

The nature of the invention: This invention relates to hydroxamic acid compounds and compositions containing the compounds, useful to treat various conditions alleviated by the inhibition of glyoxalase I.

The breadth of the claims: The claims are drawn to compounds of the Formula I



Formula I



Formula I as per elected Group VII

With independently varying variables layered with substituents on top of substituents, not to mention the stereo chemical possibilities resulting from substitutions on substitutions, the number of theoretically

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conceivable compounds for the formula is in billions, rendering the scope of the claims large, one that is not supported by the disclosure in the specification. The claims are also drawn to unknown 'solvates' of the compounds of formula I.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of organic synthesis, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction or guidance present: Three of the five generic, speculative, synthetic schemes present in the specification pertain to the making of the compounds of the elected group (see above. Note that in the elected group L2 is a single bond and X = CH). There are 7 working examples in the specification of which 4 are relevant to the elected group. All of these 4 working examples (i.e. 4 compounds) are prepared from the same aryl-mercaptan, i.e. 4-mercaptobenzyl alcohol. Thus the amount of direction present in the specification enable making compounds is extremely limited in scope. Guidance is present in the specification of making compounds of formula I wherein R1 = H, L3 = single bond, R3 = H, L4 = CH2, R4 = H *only*.

There is a complete lack of direction or guidance for procuring the crucial starting materials, i.e., the aryl mercaptans needed for making the compounds of the formula I. The specification does not provide reference to commercial source or literature citations of procedures for obtaining the starting materials. In lieu of guidance, the specification cites the generic teachings of organic chemistry text books such as, Green's Protective Groups in Organic Chemistry (see page 32 of the specification).

One of the limitations of the claims is that hydroxamic acid group is present (some where) in the molecule. The specification provides guidance for introducing this group with *one* example. i.e. by nucleophilic displacement at a benzylic situation.

The specification does not provide direction for making solvates of the compounds of formula I.

The presence or absence of working examples. The working examples present in the specification are extremely limited. There are four working examples for making the compounds (see below for use related working examples) all of which related to a single set of variables as per the elected group (see above). Of these, two are methyl and ethyl esters of the two acids. The specification claims that these esters may be prodrugs of the acids since they are hydrolyzed in cell assays. Thus, in effect, the working examples teach *two* compounds of the *billions* of possibilities for the formula I, both compounds with the same variables $R1 = H$, $L3 = \text{single bond}$, $R3 = H$, $L4 = CH_2$, $R4 = H$.

There is one example in the specification for introducing the mandatory hydroxamic acid functionality (see above). Scheme-5 in page 42, of the specification speculates on a way to introduce $R4$ aryl or $R4$ heterocyclic group by Suzuki coupling methods. There are no working examples wherein this chemistry is demonstrated.

There are no working examples of solvates of the compounds of the formula I.

The state and the predictability of the art: The state of the prior art limits whether one could use generic schemes (paper-chemistry) for making compounds with the claimed variables. The state of the art is unpredictable as to functional group compatibility during many transformations, in spite of major advances in protecting group strategies in synthesis. For instance, the variable $R1$ is recited to be among others, $-SH$, C1-4 alkyl substituted with $-SH$. The introduction of $L1-COOR6$ functionality demands that these $-SH$ groups are differentially protected in such a way that only one $-SH$ group that needs to be connected to $L1$, is available for reaction. On page 32, the specification states that protection strategies are well known in the organic synthesis for 'nonequivalent reactive functional groups'. However in practice, the realization of differentiation of 'equivalent' functional groups such as present in situation wherein $R1=SH$, needs undue amount of experimentation.

As discussed above the specification is silent about how to make the variously functionalized aryl-mercaptans. In addition, the specification is silent about many of the unpredictable limitations of the art of organic chemistry with respect to sulfur containing molecules. An example would be hydrogenation reactions wherein poisoning of metal catalysts by sulfur containing molecules requires undue

experimentations to overcome.

The state of the art is unpredictable as to the many theoretically possible reactions. The implementation of the above-mentioned Scheme-5 Suzuki-coupling to introduce a R4 groups would depend to a large extent on whether the substrates for this reaction are make-able as well as what variables are present in the aryl bromide and the boronic acid reaction partners. For instance, the art is unpredictable as to the product, if the aryl bromide of Scheme 5 contains R1 bromo group (halo is a claimed variable in the definition of R1). Such a regio-control in organic synthesis would require undue research effort.

The quantity of experimentation needed: In the instant case, there is a substantial gap between the guidance provided and the breadth of the claims. Given the direction and working Examples provided in the specification, in order to utilize the invention as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation. The guidance provided in the specification is extremely limited. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap.

The specification states on page 43, that *"when X is CH, preferably one or more of R¹, R² and R⁴ are H. More preferably two of R¹, R² and R⁴ are H, when X is CH. It is most preferred that all of R¹, R² and R⁴ are H, when X is CH"*. The disclosed examples (four compounds) in Table 1 (of page 47) conform to this stated preferred variables. The biological activities for these 'preferred' combination of variables are given in Table 2 and 3 (pages 56 and 57). Of the 4 compounds tested two had IC50s of 2 and 10 micromolar (deemed 'low IC50 values') and the inactive two compounds (esters) were deemed to be active in the cell proliferation assay (IC50s 8 and 15 micromolar). Interestingly compound E deemed active in the in vitro assay (Table 2), is inactive in the cell proliferation assay (Table 3). Thus, one of ordinary skill in the art would have to engage in undue experimentation to identify a compound encompassed by the generic formula I that would have useful activity. The instant disclosure is broad and generic and does not support the instant claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a

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hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

In conclusion, based on the evidence regarding each of the above mentioned Wands factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Nizal S. Chandrakumar



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PRIMARY EXAMINER